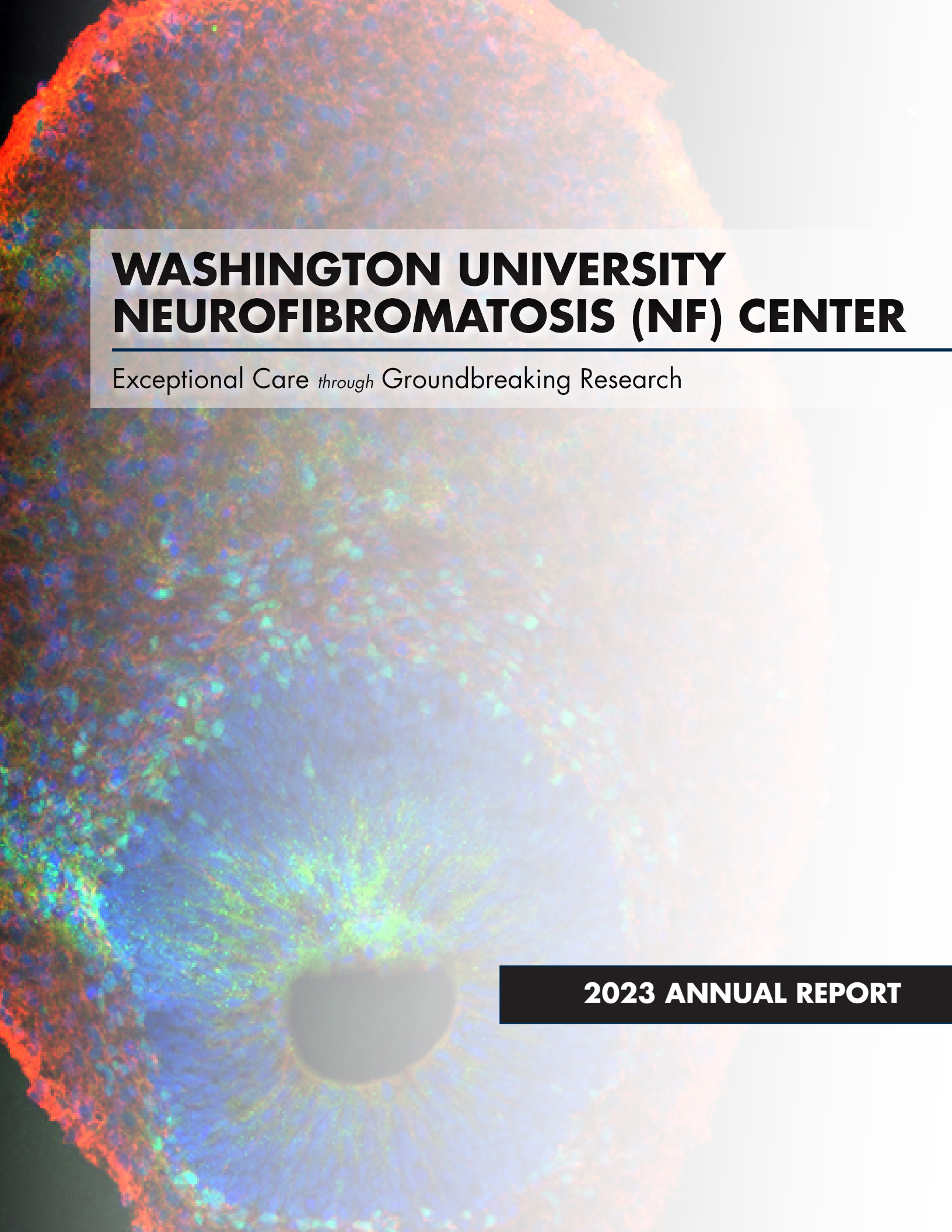

# WASHINGTON UNIVERSITY NEUROFIBROMATOSIS (NF) CENTER

Exceptional Care *through* Groundbreaking Research

## 2023 ANNUAL REPORT

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# MESSAGE FROM THE DIRECTOR

This year marks a milestone, both personally and professionally, as we celebrate 30 years of NF at Washington University. Over this period, we have witnessed the dramatic expansion of both our clinical and research programs, with the addition of new initiatives, laboratories, and patient care providers occurring on a regular basis. The dedication of our team members has culminated in the establishment of one of the world's largest and most comprehensive centers focused on improving the lives of people with NF.

## Advancing NF Clinical Care

This year, we welcomed a new adult NF neurologist, Dr. Christopher Ray, to our team. Dr. Ray joins adult neuro-oncologist, Dr. Omar Butt, and adult oncologist, Dr. Angela Hirbe, in providing outstanding care for adults with NF1 and NF2. Their addition anchors our developing adolescent/young adult transition program, which aims to assist our teenagers as they move from St. Louis Children's Hospital to Barnes-Jewish Hospital. In an effort to provide education and consultative services for physicians worldwide, together with Drs. Mohamed Abdelbaki, Director of Pediatric Neuro-Oncology, and Margaret Shatara at St. Louis Children's Hospital, we have expanded our virtual international NF Tumor Board to 32 institutions spanning 23 countries.

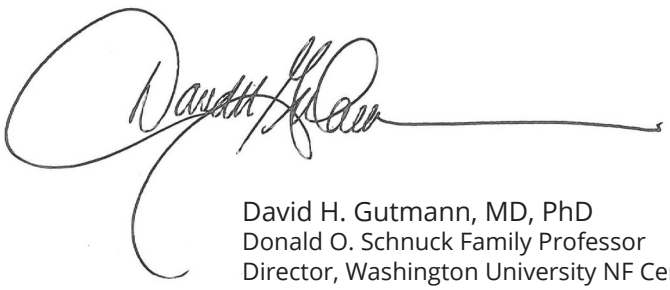
## Advancing NF Research

In the laboratory, there were also many exciting advances. Dr. Corina Anastasaki was able to develop humanized models of NF1-associated low-grade brain tumors, surmounting a significant barrier in the field. Leveraging her advance, we can establish patient-specific (personalized) brain tumors in mice using a small amount of material from patient surgery or biopsy. Additionally, Dr. Angela Hirbe and her team discovered a combination treatment that shrinks malignant peripheral nerve sheath tumors in mice, which she hopes to translate into a clinical trial for these deadly cancers in people with NF1.

## Advancing Community Engagement

Maddy Scherr, our NF Center Coordinator, has developed several new therapy programs and educational events for our families, including Camp NF and NF Family Day. She has also continued our strong partnerships with the Missouri Botanical Garden, Schnuck Markets, Jazz St. Louis, Ranken Jordan Pediatric Bridge Hospital, and the St. Louis Science Center to offer free community-based therapy events for children with NF1.

As you will read about in this annual report, there has been excellent progress on all fronts. We look forward to another exciting year of change and improvement in 2024.



David H. Gutmann, MD, PhD
Donald O. Schnuck Family Professor
Director, Washington University NF Center

# NEW RESEARCH GRANTS

## Department of Defense

- Awarded **Drs. Joshua Breunig, Yuan Pan,** and **David Gutmann** a three-year grant to define the crosstalk between brain tumor cells and non-cancerous cells in the tumor microenvironment.
- Awarded **Drs. Nicole Brossier** and **Yuan Pan** a three-year grant to investigate the relationship between diet and learning in mouse models of NF1.
- Awarded **Dr. Angela Hirbe** a three-year grant to identify predictive biomarkers for malignant peripheral nerve sheath tumors in people with NF1.

## Gilbert Family Foundation

- Awarded **Dr. David Gutmann** a three-year collaborative grant to develop tissue culture models of NF1 brain tumors. His team will work with Dr. Frank Furnari (University of California, San Diego) and Dr. Fausto Rodriguez (University of California, Los Angeles).
- Awarded **Jürgen Knoblich (IMBA, Austria)** a three-year collaborative grant to develop 3-dimensional cerebral organoid ("mini-brain") models of NF1 brain tumors. His team will work with Dr. David Gutmann (Washington University NF Center) and Dr. Fausto Rodriguez (University of California, Los Angeles).
- Awarded **Dr. Yuan Pan** a three-year grant to identify new ways to improve vision loss resulting from NF1 optic pathway gliomas.

## Hyundai Hope on Wheels

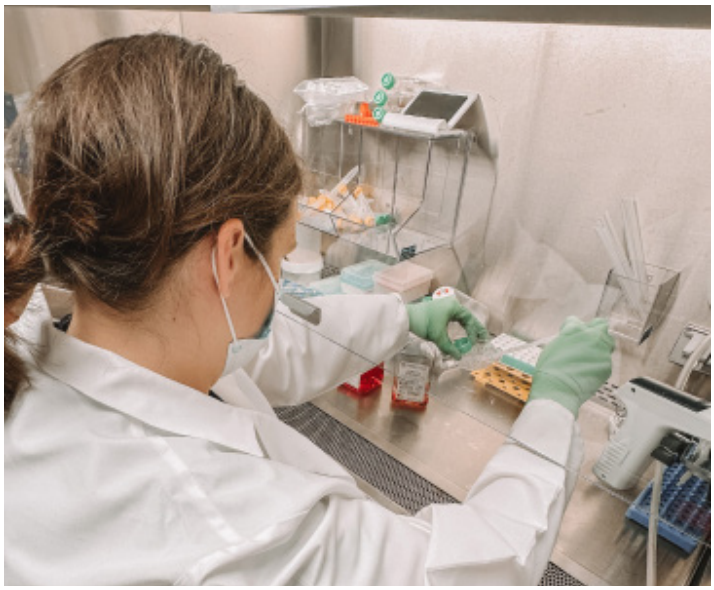
- Awarded **Dr. Amy Armstrong** a one-year grant to establish an adolescent/young adult cancer program at St. Louis Children's Hospital.

## Washington University Intellectual and Developmental Disabilities Research Center

- Awarded **Dr. Susan Maloney** a pilot grant to study learning, attention, and social deficits in mouse models of NF1.

# GROUNDBREAKING RESEARCH

During 2023, researchers in the Washington University NF Center made many groundbreaking discoveries. We continue to expand the resources required to make these advances, including the NF1 Genome Project, the NF1 Clinical Research Database, the NF1 Brain Trust, and our personalized brain tumor models program. These resources only exist because of the enthusiastic involvement of our families.



## Brossier Laboratory

Nicole Brossier, MD, PhD, is a practicing pediatric neuro-oncologist who focuses on treating children with brain and spinal tumors related to genetic disorders, including Neurofibromatosis and Schwannomatosis. Her lab focuses on understanding the genetic, neurodevelopmental, and environmental factors that influence tumor development in the pediatric brain.

## Gupta Laboratory

Located within the Institute for Informatics, Dr. Aditi Gupta employs machine learning, artificial intelligence, and advanced bioinformatic strategies to provide more personalized information about the risk of developing specific medical complications in people with NF1.

## Gutmann Laboratory

Employs NF1 as a genetic platform to characterize the genomic, genetic, cellular, and molecular factors that contribute to the development of nervous system tumors (gliomas and neurofibromas), as well as brain development and behavioral deficits.

## Hirbe Laboratory

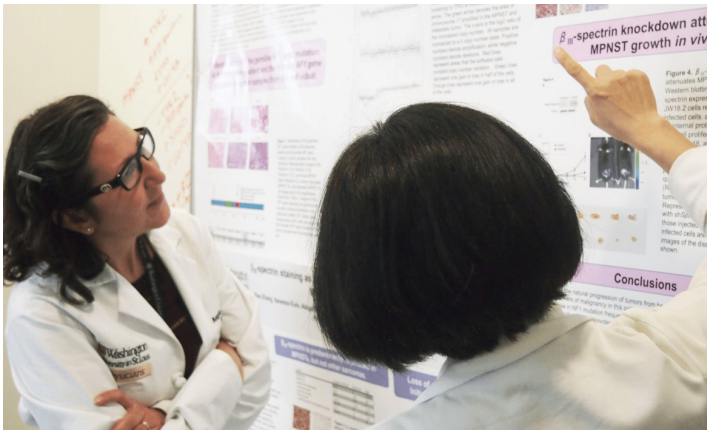
Focuses on utilizing genomic information from sarcomas to understand the pathogenesis of these tumors, identify biomarkers and discover therapeutic targets for these aggressive cancers. She launched her independent research career in 2016; since then, her laboratory has been dedicated to this work.

## Maloney Laboratory

Investigates the impact of genetic and environmental liabilities for intellectual and developmental disorders (IDD) on neural circuit function. Their projects are targeted at understanding how IDD liabilities disrupt behavior with a focus on developmental trajectories, social motivation, and sensory and motor function as they relate to core features of IDDs, and their roles in the function of the serotonin, oxytocin, and opioid systems.

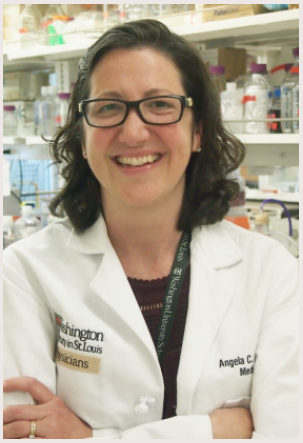
## Pan Laboratory

Located at the University of Texas MD Anderson Cancer Center, Dr. Yuan Pan's laboratory leverages primary cell culture, neuromodulatory approaches, genetically engineered mouse models, and patient-derived xenograft models to study neuron-cancer and neuron-glial interactions. They aim to provide insights into predicting, preventing, and treating nervous system cancer and neurological disorders.



## Novel Therapy for NF1 Malignant Peripheral Nerve Sheath Tumors Discovered

Leveraging prior studies from her laboratory, Dr. Angela Hirbe, Director of the Adult NF Clinical Program, identified a new potential treatment for malignant peripheral nerve sheath tumors (MPNSTs). Inhibiting the TYK2 receptor, which is overexpressed in the majority of MPNSTs, reduced the growth of mouse and human MPNST cells. Importantly, combining TYK2 inhibition with MEK inhibitors blocked the growth of MPNSTs in multiple preclinical models, establishing the rationale for developing a phase I clinical trial of deucravacitinib and mirdametinib for NF1-associated MPNST.



## MEK Inhibitor Therapy Suppresses Epilepsy in a Child With an Optic Glioma

Drs. Nicole Brossier and Judith Weisenberg reported seizure control in a child with NF1 who underwent treatment for an extensive optic pathway glioma. Based on preclinical studies in the Gutmann laboratory, MEK inhibitors like selumetinib are being evaluated in clinical trials for children with NF1-associated brain tumors.

While on selumetinib, a dose-dependent reduction in seizure frequency was observed. This report extends the positive effects of MEK inhibitor therapy on neurologic symptoms in children with NF1.

## Developing Humanized Mouse Models of Pediatric Low Grade Gliomas

Dr. Anastasaki generated human stem cells harboring *NF1* mutations, as seen in children with NF1, or expressing the KIAA1549-BRAF fusion protein commonly seen in non-NF1 low-grade gliomas. Using these lines, she identified the specific neuroglial cell populations capable of generating brain tumors, showing that neuroglial progenitors, but not astrocytes, generate low-grade gliomas in mice. She also showed that two different progenitor cell populations, glial restricted progenitors and oligodendroglial progenitors, recapitulate different histologic features of low-grade gliomas in children. She then used RNA sequencing and genetically engineered mouse strains to demonstrate that the chemokine Cxcl10 blocks tumor engraftment and growth, such that Cxcl10-deficient mice with an intact immune system can be used as hosts for establishing humanized tumor models.

Lastly, Dr. Anastasaki worked with Dr. Fausto Rodriguez, Chief of Neuropathology at the University of California Los Angeles, to grow patient-derived low-grade gliomas in mice. This advance sets the stage for ongoing work to generate precision mouse lines harboring actual patient tumors directly from the operating room.

# EXCEPTIONAL CARE


## Gutmann Inducted Into the National Academy of Medicine

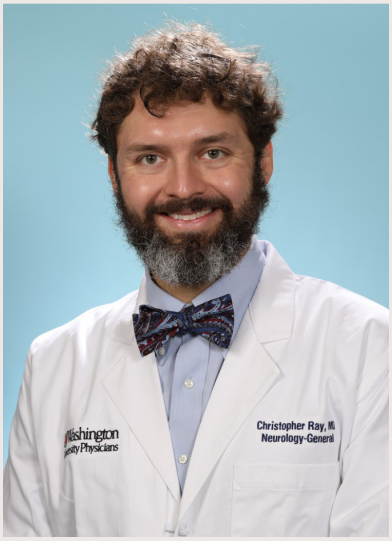
David H. Gutmann, MD, PhD, the Donald O. Schnuck Family Professor and Director of the Neurofibromatosis Center at Washington University, was inducted into the National Academy of Medicine (NAM). Induction is one of the highest honors in the fields of health and medicine. Dr. Gutmann is being recognized for his seminal contributions to the field of NF and related disorders, establishing novel human and murine preclinical model systems to elucidate the impact of germline genetics, cancer cells of origin, and the tumor microenvironment on pediatric brain tumor biology, patient risk assessment, clinical outcomes and targeted therapeutics.

NATIONAL ACADEMY of MEDICINE

## The NF Center Welcomes Dr. Christopher Ray

Dr. Ray joins the NF Center as a new Adult NF Clinical provider. He is an Assistant Professor of Neurology. He completed his residency and fellowship training at Washington University prior to becoming General Neurology and Stroke Neurology faculty. Dr. Ray strives to provide comprehensive neurological care for adults with NF, including an interest in migraine and the vascular complications of NF1. He also sees patients admitted to Barnes Jewish Hospital with strokes and other cerebrovascular diseases.

We want to thank Dr. Tiu for the exceptional care he provided our adults with NF during his tenure at the Washington University School of Medicine. We wish him the absolute best on his future endeavors.



## NF1 Clinical Program

NF experts, directed by David H. Gutmann, MD, PhD, provide detailed patient assessments while working with referring physicians, allied health professionals, and agencies to deliver cutting-edge medical services both locally and nationally. Our team-based approach leverages the expertise of NF experts (Dr. Gutmann, Sheel Pathak, MD, Erika Ramirez, BSN, RN, and Madeline Scherr, MS, OTR/L), dedicated NF subspecialists (Drs. Amy Armstrong, Nicole Brossier, Angela Hirbe, Omar Butt, Christopher Ray) and numerous other clinical practitioners in therapy services, neuropsychology, neurosurgery, neuro-ophthalmology, neuropathology, orthopedics, plastic surgery, and genetics to treat NF patients of all ages.

## Adolescent and Young Adult (AYA) Clinical Program

One of the major hurdles for our young adults is transitioning their care to the adult hospital. In order to facilitate this transition and to provide resources for our teenagers, we have established a three-pronged approach. This includes an active survey-based clinical study to define the needs of our young adults, the institution of a stepwise plan, beginning at 14 years of age to define annual goals towards medical care independence, and providing overlapping transition visits between pediatric and adult providers.

## NF2 / Schwannomatosis Clinical Program

Individuals with Neurofibromatosis Type 2 (NF2) / Schwannomatosis (SWN) can benefit from the midwest's only program specializing in NF2/SWN patient care – the Washington University NF2/SWN Clinical Program. This program is a joint project of the Washington University NF Center and the Alvin J. Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine. Care is provided by Drs. Greg Zipfel, Albert Kim, Craig A. Buchman, and Omar Butt. Their collective experience in treating large numbers of patients with this uncommon disease galvanized the assembly of this team of experts aimed at providing specialized care tailored to patients diagnosed with NF2/SWN.

# PATIENT SPOTLIGHT

## *Harper Grace Durham*

When Harper Grace was a few months old, we found out that she had an optic pathway glioma and a brain biopsy was needed. This ultimately confirmed her NF1 diagnosis. When we first received the news about Harper having NF1, Harper's Dad did tons of research. He called the Children's Tumor Foundation and asked who the best NF doctor in the country was. Their answer was "The NF Center at Washington University in St. Louis Missouri." How blessed are we that the very best was in our backyard? The NF Center has been there for our family for questions, referral letters, assistance with school and therapy scripts, research on genetic testing, and fun events to help our little girl feel like a regular kiddo. We know they have our daughter's best interest in mind and we appreciate all they do for her.

Harper loves that everyone treats her like a star at the NF Center! The staff is kind and takes time to talk with her, not just her parents. She is able to be part of the visits and play a role in all that happens. They don't rush and they make her feel comfortable and important. Harper enjoyed NF day at the Botanical Gardens, music therapy with Jazz St. Louis, and is pumped for her first NF Summer Camp coming up soon!

When Harper was first diagnosed and going through chemo, a Go Fund Me was set up for her which helped with medical bills. A year later when she had to add a shunt and found herself in more hospital stays, another donation window was created. Also during chemo, Harper's mom taught a charity dance class which students from all over Missouri came in to support Harper Grace and donations were made in Harper's honor. The event brought in significant funds to assist with unexpected treatment costs. Since that time, many friends and family will donate items and food to help during unexpected hospital stays for Harper girl. We have also searched for organizations to donate an assistive bike, give Harper experiences, and offer gift cards, food, and other resources for our family. Our family tries to give back to organizations as much as possible to raise NF awareness and help others like Harper. We have asked that people donate to the NF Center in Harper's honor, we have walked in and raised money for Children's Tumor Foundation to raise money for NF research, our family participates in Friends of Kids With Cancer fundraising and charity runs, we have run and raised money for the Give Children The World Village from Harper's Make-A-Wish trip, we support Pedal The Cause, and plan to continue our effort to let people know about NF and all of amazing resources and people that are out there helping so many children and families.

You can follow her journey on her Facebook page, **Healing Harper.** Thank you to the NF Center for supporting our daughter and family. Navigating this new normal has been an adventure and you have been a wonderful constant. We appreciate you!

*#HealingHarper #HarperStrong #ikNowaFighter*

# TRAINING OPPORTUNITIES

Trainees at all levels, from undergraduates to graduate students and beyond, are welcome to participate in research and development opportunities through the Washington University NF Center.

### Post-Baccalaureate Students

Students interested in laboratory research between undergraduate and graduate school are hosted as part of the Postbaccalaureate Program in Developmental Biology & Regenerative Medicine Program at Washington University.

### Medical and PhD Graduate Students

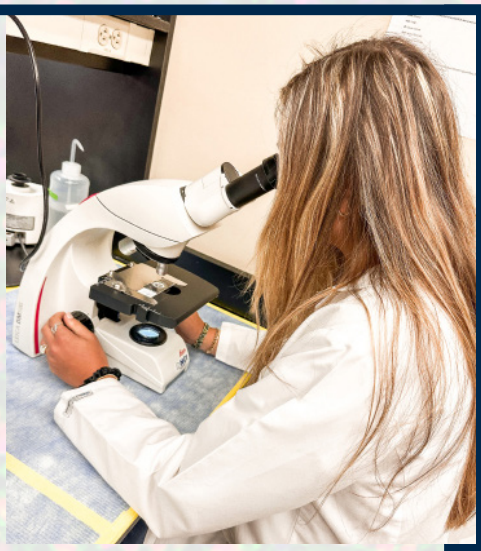
Washington University medical students have numerous opportunities to participate in laboratory research, as well as to obtain PhD or MD-PhD graduate training.

### Postdoctoral Fellows

Formal training opportunities are available for motivated PhD researchers and physician-scientists to develop careers in disease-oriented investigation.

## NF Scholars Program

The future of NF research and clinical care is dependent on attracting future physicians/scientists at an early stage of their training. Unfortunately, the opportunities for early engagement in laboratory or clinical research are not equally available for all interested students. To address this need, we established a comprehensive training curriculum, the NF Undergraduate Scholars Program, that begins during the early college years, and includes mentorship, group team learning, professional development, and two years of laboratory or clinical research, with the option of completing an honors thesis at Washington University.



# COMMUNITY INVOLVEMENT

We believe that the care of our families extends beyond the walls of the hospital. To supplement our medical services, we have developed free therapy programs for children of all ages. Our goal with each program is to foster an environment of teamwork and friendship where children can learn and develop skillsets that are often delayed in people with NF1. This year, we were able to introduce two new programs, Camp NF and NF Family Day, which allowed us to reach a larger NF1 population.

## Music Heals (Ages 1 – 5 years)

In affiliation with Ranken Jordan Pediatric Bridge Hospital and Jazz St. Louis, Music Heals is a jazz music therapy program for young children of all abilities. The curriculum is designed to improve social, sensory, and motor skills, while fostering healthy parent-child interactions.

## Club NF (Grades K – 8)

Club NF is a play-based therapy program for children with NF1. Events are held bi-monthly at various places across the St. Louis region and are designed to address a specific set of skills often delayed in school age children with NF1. Examples of past events include cooking, ice skating, and glass making.

## Totally TEEN (Ages 13 – 18 years)

To help teenagers gain independence, we developed Totally TEEN (Thrive. Engage. Educate. Neurofibromatosis.). Led by Maddy Scherr, NF Center Occupational Therapist, sessions focus on choosing appropriate friends and social activities, exploring career interests, money management, and food preparation. Each event is held at a different location across the Greater St. Louis area, such as Topgolf, the St. Louis Science Center, and Schnucks Cooking School.


## Camp NF (Grades K - 8)

Through amazing community partnerships, we were able to introduce Camp NF this summer. Hosted at an outpatient therapy clinic and in collaboration with a nonprofit music therapy organization, children with NF1 had the opportunity to work on various developmental skills in a fun and interactive environment. Using sensory swings, musical instruments, and motor activities, children of various ages left camp with new found skills and friendships. A special thank you to Acorn Children's Therapy and The Song Society.

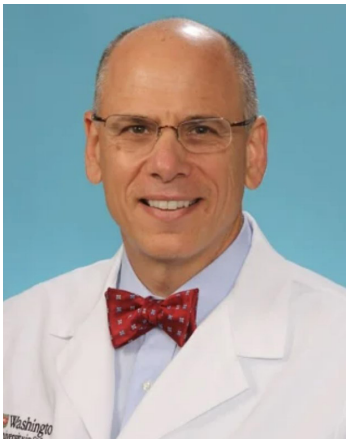
## NF Family Day (All ages)

This summer, the Missouri Botanical Garden opened its doors for the Washington University NF Family Day. This was the NF Center's first event of its kind, and it was an overwhelming success! From a scavenger hunt and splash pad to potting a plant and painting, the NF Family Day included therapy experiences for all ages. In addition, we appreciated the amazing guest speakers who donated their time to provide information about Individualized Education Plans (IEPs). It was great to see the smiles and hear the laughter from our patient families. A special thank you to the Missouri Botanical Garden, Missouri Disability Empowerment, and Bright Paths Advocacy.

For the past 30 years, the NF Clinic at St. Louis Children's Hospital, has helped numerous individuals with NF1, NF2, and Schwannomatosis. None of this would be possible without our incredible clinical faculty.

**Dr. Amy Armstrong, MD**
Assistant Professor of Pediatrics

**Dr. Nicole Brossier, MD, PhD**
Assistant Professor of Pediatrics



**Dr. Craig Buchman, MD, FACS**
Chair, Department of Otolaryngology—Head & Neck

**Dr. Omar Butt, MD, PhD**
Assistant Professor of Neurology

**Dr. David Gutmann, MD, PhD**
Director, NF Center

**Dr. Angela Hirbe, MD, PhD**
Director, Adult NF Clinical Program

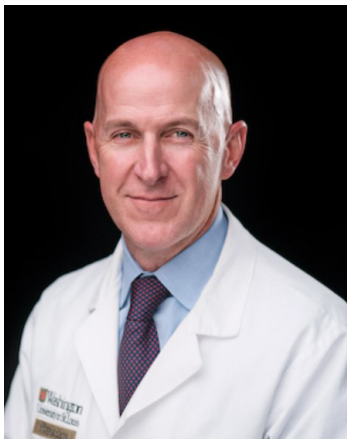
**Dr. Albert Kim, MD, PhD**
Professor of Neurosurgery
Director, Brain Tumor Center

**Dr. Sheel Pathak, MD**
Assistant Professor of Neurology and Pediatrics

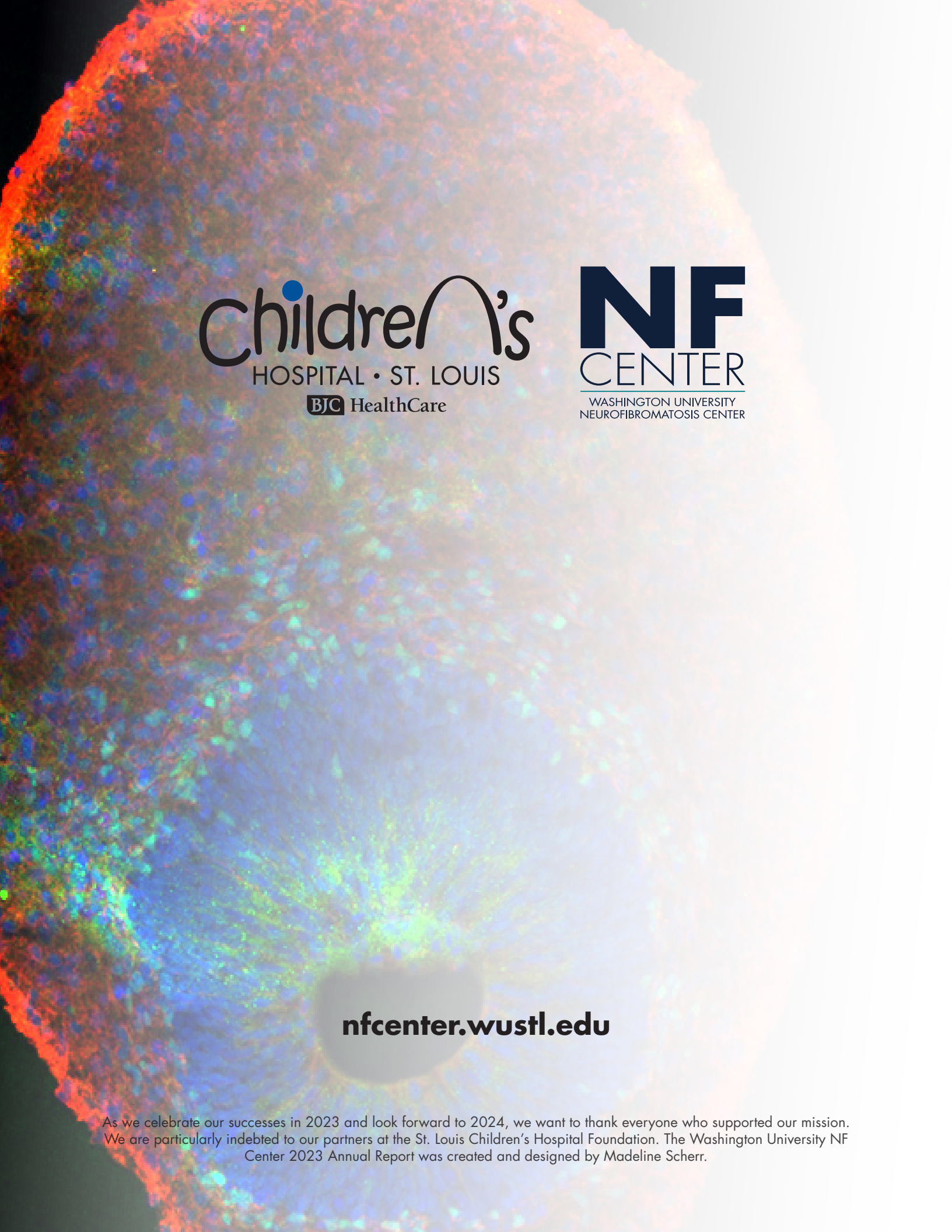
**Erika Ramirez, RN, BSN**
NF Center Clinical Nurse Coordinator

**Dr. Christopher Ray, MD**
Assistant Professor of Neurology

**Madeline Scherr, MS, OTR/L**
NF Center Coordinator
Occupational Therapist



**Dr. Gregory Zipfel, MD**
Chair, Department of Neurosurgery



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**nfcenter.wustl.edu**

As we celebrate our successes in 2023 and look forward to 2024, we want to thank everyone who supported our mission. We are particularly indebted to our partners at the St. Louis Children's Hospital Foundation. The Washington University NF Center 2023 Annual Report was created and designed by Madeline Scherr.